REVIEW

Benefits of Remote Ischaemic Preconditioning in Vascular Surgery

C.P. Twine [a,*], S. Ferguson [b], J.R. Boyle [b]

[a] South East Wales Vascular Network, Royal Gwent Hospital, Newport, UK
[b] Addenbrooke's Hospital, Cambridge, UK

WHAT THIS PAPER ADDS

Remote ischaemic preconditioning (RIPC) is a physiological mechanism to protect against ischaemia—reperfusion injury. Interest in the technique has exploded in recent years, with multiple randomised trials and meta-analyses on the subject being published. This is the first article to summarise the physiology, and critically appraise the technique, trials and meta-analyses to date.

Objectives: Remote ischaemic preconditioning (RIPC) is a physiological mechanism to protect against ischaemia—reperfusion injury. It is a technique in which short pre-emptive periods of ischaemia and reperfusion are thought to protect against ischaemia—reperfusion injury during procedures requiring longer periods of ischaemia. Discovered in the 1980s, its clinical application has been investigated heavily since the first human study in 2006. The aim of this paper was to provide a review of this rapidly expanding subject.

Methods: This study consists of a narrative review of the literature focusing on previous meta-analyses and randomised control trials.

Results: Five small randomised trials have been published on the effects of RIPC in vascular surgery. Several randomised trials have been published in cardiac surgery and percutaneous coronary intervention. Meta-analysis shows a significant reduction in troponin levels and biomarkers of renal dysfunction in RIPC patients, but as yet no convincing clinical benefit. The largest powered randomised trial in cardiac surgery showed no benefit to RIPC.

Conclusions: Current trials and therefore meta-analyses are generally underpowered. The technique is physiologically sound but remains lacking in clear clinical benefit.

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INTRODUCTION

Remote ischaemic preconditioning is one of the most investigated topics in modern vascular medicine. Myriad randomised trials have already been undertaken and 92 are still registered or actively recruiting on ClinicalTrials.gov (search date December 2013). The majority of these trials were essentially pilot studies, reporting a variety of different outcomes, and provided little evidence of actual clinical benefit. Meta-analyses would therefore be expected to be of limited use, although a staggering 10 have been published from these trials within the last 2 years.[1–10]

There is, however, sound scientific theory and the potential of greater things to come from remote ischaemic conditioning (RIPC) within this literature. The aim of this topical review was to critically appraise and put the evidence for this technique in a clinical context.

* Corresponding author. C.P. Twine, Royal Gwent Hospital, Cardiff Road, Newport NP20 2UB, UK.
E-mail address: chris_twine@hotmail.com (C.P. Twine).

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Remote ischaemic preconditioning in clinical practice

RIPC is a technique in which short pre-emptive periods of ischaemia and reperfusion are thought to protect against ischaemia—reperfusion injury during procedures requiring longer periods of ischaemia. It is therefore of interest in vascular surgery where the majority of procedures require periods of ischaemia, and is relatively easy to perform.

For example, during open abdominal aortic aneurysm repair the common iliac could be clamped for 5 minutes immediately after access to the peritoneal cavity. The aortic dissection would proceed normally during this time period. After this time the clamp is released, so a short period of ischaemia—reperfusion has occurred. The same effect may be achieved using a tourniquet on the thigh. A degree of RIPC may happen when proximal control of target vessels is achieved in open vascular surgery. This is thought to "remotely" precondition every organ in the body against ischaemia—reperfusion injury before the longer periods of more extreme ischaemia the operation will then require. This is then believed to limit the dysfunction of other organs, such as the kidneys and heart, caused by reperfusion.

Ischaemic preconditioning discovery and mechanisms of action

Ischaemic preconditioning is a physiological mechanism to protect against ischaemia–reperfusion injury. It was discovered in the 1980s by a team investigating adenine triphosphate depletion (ATP) in myocytes.[11] They were investigating mechanisms of ATP depletion and lactic acidosis leading to myocyte death. They initially presumed that by exposing mammalian cardiac tissue to brief episodes of ischaemia then reperfusion, they would deplete ATP and lactate would accumulate at a constant rate. However, instead they found that ATP actually depleted to a certain critical level then stabilised during brief ischaemia–reperfusion cycles. At the same time, lactate production was depressed. Observing this, they hypothesised that cell death could be prevented by ischaemia–reperfusion cycles. They were correct: cumulative cycles of ischaemia–reperfusion allowed myocytes to survive far longer than the 40 minutes seen in non-preconditioned myocytes. Preconditioning preserved ATP levels, depressed lactate levels and delayed cell death by a significant period of time.[12]

The mechanism for this is still not fully understood. Adenosine produced during the first preconditioning cycle appears to be the trigger for protection as rabbit hearts exposed to adenosine show the same preconditioned effect as with short cycles of ischaemia.[13] Although the adenosine signalling cascade from the sarcolemma has been studied in detail, the resulting changes in ATP and lactate production in the cell are still not understood.

From this point, research showed that when a different organ, even skeletal muscle, was used for ischaemic preconditioning it still conferred benefit to myocytes.[14] This was termed remote ischaemic preconditioning (RIPC). It was then a short step to human trials, as inducing skeletal muscle ischaemia with a tourniquet is a relatively low risk procedure. The first human study was in children undergoing congenital cardiac defect repair surgery.[15] Thirty-seven patients were randomised to RIPC or no RIPC. They found significantly lower levels of troponin ($p = .04$) and lower postoperative inotropic requirements ($p = .03$) in the RIPC group.[15]

By this time, interest in the technique was exploding, as were pilot randomised trials. Trials were easy to perform, low risk, and easy to power with relatively low patient numbers. Although the initial trials examined cardiac markers in cardiac surgery, this was soon extrapolated to the cardiovascularly high-risk procedure open abdominal aortic aneurysm (AAA) repair.[16] Observations of changes in renal function during that trial led to specific studies examining renal injury.[17] The same group then went on to perform several trials examining the effects of RIPC in other vascular surgical procedures, which are discussed in detail below. Research also continued examining RIPC in percutaneous and open cardiac intervention.

Evidence in AAA

Three randomised trials have examined the effects of remote ischaemic preconditioning in elective open AAA repair,[16–18] and one examined endovascular aneurysm repair (EVAR).[19] The open AAA studies performed limb RIPC by iliac clamping, and the EVAR trial used a lower limb tourniquet. These small, pilot studies were powered to detect differences in myocardial injury,[16,18,19] kidney injury,[17,19] and intestinal and pulmonary dysfunction defined predominantly by biomarkers.[16] Three of the four trials were performed at Addenbrooke's Hospital in Cambridge.[16,17,19]

Ali et al.[16] examined the effect of RIPC on 82 patients undergoing elective open AAA repair. They found a reduction in both troponin levels ($p = .005$) and myocardial infarction (MI) ($p = .006$: defined here by troponin and electrocardiogram changes but without chest pain) in the RIPC group. However, they powered the study for troponin levels and do not discuss the clinical outcomes of the significant findings. They also found a reduction in renal impairment ($p = .009$) in the RIPC group. Renal impairment was defined here using creatinine levels (rising to >177 µmol/L). There were, however, more (non-significant) suprarenal cross-clamps in the non RIPC group. Again, the study was not powered to detect changes in creatinine. Definitions of renal failure vary by study and therefore introduce significant heterogeneity into meta-analysis.

The group therefore followed up this trial by examining the effect of RIPC on renal failure in open AAA,[17] while at the same time examining the cardiac and renal effects of RIPC in EVAR.[19] Powered to detect changes in postoperative renal dysfunction after open AAA, the open AAA trial randomised 40 patients and found that there was no difference after RIPC ($p = .07$). This included both urinary biomarkers and albumin–creatinine ratios. The EVAR trial was again powered for renal dysfunction, but this time found a significant reduction in the urinary biomarker retinol-binding protein ($p = .0001$). There were, however, no differences in creatinine levels or cardiac complications in the 40 patients randomised.

The most recently published small RCT was from China.[18] The authors examined intestinal and pulmonary dysfunction (arterial–alveolar oxygen tension ratio) after open AAA repair in 62 patients. They found a significant improvement in pulmonary function in the RIPC group ($p = .039$) and a reduction in biomarkers ($p < .001$) and clinical grade ($p = .014$) of intestinal injury. Meta-analysis of these studies is discussed below.

Evidence in other vascular surgery

The Cambridge group also examined the effect of RIPC during carotid endarterectomy.[20] This pilot study examined cerebral and cardiac protection via RIPC performed with a thigh tourniquet, and randomised 70 patients. The trial was powered to detect changes in saccadic latency (the time taken to respond and fix on a visual stimulus that appears suddenly) rather than myocardial infarction. They found no difference in stroke (no strokes during the trial, no differences in saccadic latency $p = .11$) or cardiac outcomes ($p = .97$) during the trial.

Meta-analysis

Meta-analysis of the four "pure" vascular trials published before 2011[16,17,19,20] (1 trial has been published since[18]) showed an improvement in myocardial infarction (defined predominantly by troponin changes) in the RIPC group but no improvement in mortality, renal failure, or hospital stay, as well as clinically relevant myocardial infarct (Table 1).[4] The highest quality meta-analysis published on RIPC included vascular and cardiac trials.[2] This showed an improvement in biomarker-defined myocardial infarction but no difference in mortality, renal failure, major cardiac events (including more clinically relevant definitions of myocardial infarction), or length of stay.[2] The final two meta-analyses in Table 1 were of lower quality and capture fewer trials than the higher quality analyses.

Interestingly, the largest RCT examining AAA[16] was a significant outlier in the cardiovascular event Forest plot of the largest meta-analysis.[2] This was the only trial with a

Table 1. Meta-analyses including vascular studies of remote ischaemic preconditioning.

Author	Year	Trials included	Number of studies (participants[a])	Type of study	Major findings (OR, SMD, and 95% CI)	Risk of bias from included studies
Desai et al[4]	2011	Vascular and endovascular	4 studies (232 [115:117])	RCT	RIPC improved: Myocardial infarction[b]: (OR 0.31 [1.10–0.90] $p = .03$) No improvement: Mortality: (OR 1.70 [0.91–5.92] $p = .39$) Renal failure: (OR 0.74 [0.35–1.54] $p = .42$) Hospital stay: (SMD −0.12 [−2.38–2.13] $p = .91$)	Low
Brevoord[2]	2012	Vascular, endovascular, open cardiac surgery, percutaneous cardiac intervention	23 studies (1878 [954:924])	RCT	RIPC improved: Myocardial infarction[b]: (OR 0.50 [0.31–0.82] $p = .005$) Peak troponin levels: (SMD −0.28 [−0.47 – −0.09] $p = .003$) No improvement: Mortality: (OR 1.22 [0.48–3.07] $p = .68$) Renal failure: (SMD 1.88 [5.10–8.87] $p > 0.05$) Major cardiac events: (OR 0.65 [0.38–1.14] $p = .13$) Length of stay: (SMD 0.04 [−0.21–0.29} $p > 0.05$)	Moderate
Li et al.[5]	2013	Vascular, endovascular, open cardiac surgery, percutaneous cardiac intervention	10 studies (924 [464:460])	RCT	No improvement: Mortality: (OR 1.21 [0.49–2.97] $p = .68$) Renal failure: (OR 0.73 [0.50–0.64] $p = .18$) Length of stay: (SMD 0.07 [−0.50–0.64} $p = .81$)	Moderate
Takagi and Umemoto[7]	2011	Vascular and open cardiac	9 studies (488 unclear)	RCT	RIPC improved: Peak troponin levels: (SMD −0.74 [−0.97 to −0.52] $p < .00001$) No improvement Myocardial infarction[b]: (OR −0.02 [−0.06–0.02] $p = .28$) Mortality: (OR 0.01 [−0.03–0.05] $p = .65$)	Moderate

RCT = randomised controlled trial; RIPC = remote ischaemic preconditioning; SMD = standardised mean difference.

[a] Preconditioned–non-preconditioned.

[b] Defined predominantly by troponin levels.

strong positive result in favour of RIPC reducing cardiac events. This study included 41 patients in each arm, and was small compared to some trials of open cardiac surgery which contained >100 patients in each arm. Myocardial infarction was broadly defined in this study by cardiac troponin I (>0.40 ng/mL), and by the American College of Cardiology/American Heart Association definition.[16]

The likely reason for the significant findings in favour of RIPC during open AAA therefore starts to look like type 1 error from underpowered trials. This is known to be a problem when meta-analysing small randomised trials.[21] An example of this phenomenon is the significant improvement seen in postoperative troponin levels in the RIPC group defined as 'myocardial infarction" in some trials (Table 1). This translated into a non-significant difference when this result was examined as major adverse cardiac events, which is far more clinically useful. Further evidence of the relatively poor overall quality of these trials was the finding of a moderate overall risk of bias in all of the largest meta-analyses.[22] It must be remembered that these were, by their own admission, pilot studies.

However, the main question raised when trying to draw meaningful conclusions from these analysis is: How relevant is it to meta-analyse these trials together? They include a clinically heterogeneous group of procedures which are not directly comparable. Major adverse cardiac events are far more common after open AAA and open cardiac surgery than after percutaneous coronary intervention. Similarly, is it relevant to include a study of carotid endarterectomy with such trials? Performing meta-analysis in this manner leads to high heterogeneity between studies, seen here especially in major adverse cardiac events and troponin release analyses.[2,5,7] A lack of heterogeneity during meta-analysis of small trials suggests that trials are simply underpowered to detect differences for that outcome, the best example in these meta-analyses being mortality rate analyses.[2,5,7]

The results from these meta-analyses are therefore not particularly useful and only really serve to proclaim that which is obvious looking at the source data: further properly powered randomised trials are needed to test whether RIPC is actually of any clinical use.

Interestingly, a recent large randomised trial of RIPC in cardiac surgery has shown no benefit. A total of 1,280 patients undergoing elective cardiac surgery were randomised to RIPC (644 patients) or no RIPC (636 patients). The RIPC was via an arm tourniquet. The trial showed no difference in in-hospital mortality ($p = .392$), cardiac ($p = .746$), renal ($p = .775$), or stroke ($p = .978$) complications.[23] This may be a reflection of what is to come when the properly powered vascular trials report in the future.

Future research

Other larger trials have been set up and are now recruiting. For example, the SAVES study (Preconditioning Shields Against Vascular Events in Surgery) is a large, multicentre trial aiming to enrol 1,900 vascular patients to examine major adverse clinical events. The ERIPCCA study (Effect of Remote Ischaemic Preconditioning on Clinical Outcomes in CABG Surgery) is aiming to recruit 1,610 cardiac patients to examine multiple effects, primarily major adverse cardiac and cerebral events. These trials should answer the question of whether RIPC improves clinical outcomes much more thoroughly than the pilot studies already performed.

Summary

Ischaemic preconditioning is a physiological mechanism to protect against ischaemia—reperfusion injury. Mediated by adenosine, cycles of ischaemia and reperfusion preserve intracellular ATP levels, prevent lactate build up, and delay cell death. Once it was discovered that the ischaemia required to drive this protection in cardiac myocytes could be performed in other organs, including skeletal muscle, the concept of remote ischaemic preconditioning was born. Published clinical trials are currently essentially pilot studies which broadly show reduction in various biomarkers of organ injury but were not large enough to detect true clinical outcomes. Meta-analysis of these trials is therefore statistically flawed, but still abundantly popular in the literature.

Importantly, RIPC is cheap, safe, easy to perform, and scientifically sound on a physiological level. Larger trials that will answer the question as to whether this will translate into clinical benefit are recruiting. The results from the first of these, however, showed no benefit to RIPC.

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CONFLICTS OF INTEREST

J.B. was involved in several of the randomised trials discussed.

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